



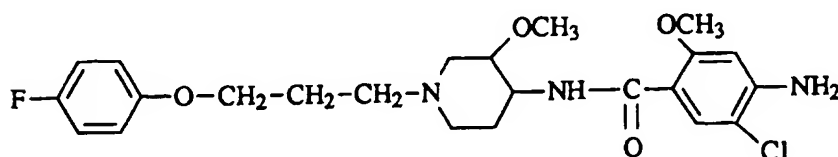
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(21) International Application Number: PCT/EP95/04198 (22) International Filing Date: 25 October 1995 (25.10.95) (30) Priority Data: 94203184.0 2 November 1994 (02.11.94) EP (34) Countries for which the regional or international application was filed: DE et al. (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): JANS, Eugene, Marie, Jozef [BE/BE]; Rodekruislaan 3, B-2450 Meerhout (BE). GILIS, Paul, Marie, Victor [BE/BE]; Schransdriesstraat 14, B-2340 Beerse (BE).		(81) Designated States: AL, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LS, LT, LV, MD, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: CISAPRIDE EXTENDED RELEASE ORAL COMPOSITIONS (57) Abstract The present invention concerns extended release formulations comprising cisapride-(L)-tartrate, in particular an oral formulation, the use thereof as a medicine, especially in treating gastrokinetic disorders.		

Cisapride extended release oral compositions

- 5 The present invention concerns extended release formulations comprising cisapride-(L)-tartrate, in particular for oral administration, the use thereof as a medicine, especially in treating gastro-intestinal disorders.

- 10 European Patent No. 0,076,530 discloses the gastroprokinetic agent cisapride and classic compositions thereof. Cisapride has the following structural formula :



- 15 The systematic chemical name of cisapride is cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide. Cisapride is a racemic mixture of two enantiomers. Cisapride has excellent gastro-intestinal motility stimulating properties and is reported to be devoid of antidopaminergic activity. Its utility in a variety of gastro-intestinal disorders has already been reported extensively.
- 20 Useful extended release formulations of cisapride for oral administration should release the active ingredient, i.e. cisapride, over a long period of 15 to 24 hours, that is through the whole gastro-intestinal tract with its varying pH values. However, the solubility of cisapride depends very much on the surrounding pH. The solubility of cisapride is the highest in a strongly acidic medium at pH 1 to 2, such as for example in gastric juice.
- 25 The solubility diminishes rapidly when the pH of the (physiological) medium increases, for example in the intestines. An effective sustained release formulation of cisapride should therefore function not only in highly acidic but also in less acidic or neutral media. Moreover an extended release formulation should release the active ingredient as soon as the formulation is administered and should release the active ingredient in a
- 30 constant manner, preferably following zero order to first order kinetics. This profile is desired because it provides relief to the patient very soon after administration and overdosing is avoided when administering the formulation for a consecutive time.

- 35 A solution to this problem was found in the use of (+)-cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide [R(R*,R*)]-2,3-dihydroxybutanedioate (1:1) - referred to hereinunder as "cisapride-(L)-tartrate" - in

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a matrix formulation as described hereinafter. Cisapride-(L)-tartrate is the salt of racemic cisapride with (+)-L-tartaric acid and is exemplified in European Patent No. 0,076,530 as compound number 241.

5 An additional aspect of this invention is the fact that the production process for the present extended release formulations is very simple as is shown in the examples hereinunder. This is in contrast to the production processes known in the art for preparing extended release formulations.

10 In comparison with other salts of cisapride the salt form with [R(R*,R*)]-2,3-dihydroxybutanedioic acid, i.e. (+)-L-tartaric acid (the natural form of tartaric acid) shows a remarkably good solubility in water. Cisapride being a racemic mixture and L-tartaric acid being one single enantiomer, the resulting salt form is in principle a mixture of two diastereomeric salts : (+)-cisapride-(L)-tartrate and (-)-cisapride-(L)-tartrate.

15 Unexpectedly, it was shown that the salt cisapride-(L)-tartrate is a mixture of the diastereomers [(3R4S)(2R3R)] and [(3S4R)(2R3R)], that crystallize as a double salt in a 1:1 ratio. (This is confirmed by X-ray.) The (3R4S) and (3S4R) refer to the respective enantiomers of cisapride and the (2R3R) refers to the optically pure L-tartrate.

20 Unexpectedly, it was found that formulations containing cisapride-(L)-tartrate released cisapride in a racemic form, i.e. equal amounts of (+)-cisapride and (-)-cisapride or in other words the diastereomeric salt forms (+)-cisapride-(L)-tartrate and (-)-cisapride-(L)-tartrate unexpectedly have equal dissolution rates.

25 Moreover, it was also found that during the preparation of cisapride-(L)-tartrate no enrichment of one of the two diastereomeric salt forms could be detected.

30 Compositions according to the present invention comprise pharmaceutically acceptable carriers and excipients, such as fillers, e.g. lactose, sucrose, mannitol, maize starch, preferably lactose; lubricants e.g. stearic acid, magnesium stearate, talc or silica or mixtures thereof; preferably a mixture of magnesium stearate, talc and colloidal silicon dioxide (Aerosil ®). Also other pharmaceutically acceptable additives such as colorants or flavorings and the like may be present.

35 The "retard"-effect or "extended release" effect is due to the fact that the cisapride-(L)-tartrate is embedded in a mixture of two viscous polymers. Hence, the formulation

comprises a mixture of a highly viscous hydrophilic polymer and a viscous hydrophilic polymer, which releases the active ingredient gradually from the formulation. For the present active ingredient, cisapride-(L)-tartrate, this can conveniently be achieved using a mixture of hydroxypropyl methylcellulose and another viscous cellulose derivative such as, hydroxypropylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxyethyl methylcellulose, methylcellulose, preferably hydroxypropylcellulose.

These two hydrophilic polymers swell when in contact with water, thus creating a porous matrix from which the cisapride can gradually be released. The said polymers themselves also dissolve slowly in the aqueous medium. Consequently, the surface of the formulation is also constantly dissolving and so the aqueous medium can reach the more inward mixture of polymers, that in turn begins swelling and releasing active ingredient thus providing for a continuous release of active ingredient following a zero order to first order kinetics.

The hydroxypropyl methylcellulose used in the above mentioned mixture preferably has a viscosity of about 15,000 mPa.s, e.g. hypromellose 2208.

The hydroxypropylcellulose used in the above mentioned mixture should preferably have a viscosity ranging from 150 to 700 mPa.s, preferably from 200 to 600 mPa.s, e.g. Klucel EF ®.

The relative amount of said mixture of viscous hydrophilic cellulose polymers in a formulation ranges preferably between 15 % and 35 % of the total composition weight. The relative amount of mixture of viscous hydrophilic cellulose polymers correlates with the period during which the active ingredient is released. The lowest limit, i.e. 15 %, gives a reasonably extended release period of about 900 minutes. The highest limit, i.e. 35 % leads to longer release periods yet still releasing all of the active ingredient present in the formulation. At relative amounts higher than 35 % there is expected to be an incomplete release of the active ingredient.

The ratio of the weight hydroxypropyl methylcellulose over weight of the other cellulose polymer ranges from 0.33 to 3. In particular the ratio of the weight of hydroxypropyl methylcellulose over the weight hydroxypropyl cellulose ranges from 0.33 to 3. The preferred ratio is 1, i.e. equal amounts of hydroxypropyl methyl cellulose and hydroxypropylcellulose are present.

The preferred oral formulation of the present invention is a tablet.

Said tablets may have different kinds of shapes, e.g. oblong or right circular. The shape of the tablet influences the release period, because of the fact that different shapes have a different ratio of surface over volume.

5

A person skilled in the art will appreciate that the volume of the tablet is function of other parameters such as, the actual composition, shape, intended period of release and the intended dose. The exemplified compositions are given for right circular tablets with a diameter of about 11.5 mm diameter and a height of about 5.2 mm.

10

Said tablets may have lines or break-marks and may bear a symbol or other markings.

Said tablets can optionally be coated with art-known coating compositions. Coated tablets are the preferred formulation in this invention. The above ingredients and ratios apply for the "formulation-core" in general, the "tablet-core" in particular. the compositions of these "formulation-cores" will be called core-compositions hereinafter.

15

Suitable coating formulations comprise a filmforming polymer such as, for example, hydroxypropyl methylcellulose, e.g. hypromellose 2910 (5 mPa.s); a plasticizer such as, for example, a glycol, e.g. propylene glycol; an opacifier, such as titanium dioxide; a film smoother, such as talc. Water is added as a solvent.

20

Suitable core compositions are :

25

cisapride-(L)-tartrate :	from 2 to 15 % by weight
filler :	from 50 to 70 % by weight
hydrophilic polymer mixture :	from 15 to 35 % by weight
lubricants :	from 0.5 % to 10 % by weight

30

Interesting core compositions are :

cisapride-(L)-tartrate :	from 5 to 15 % by weight
filler :	from 50 to 70 % by weight
hydrophilic polymer mixture :	from 15 to 35 % by weight
lubricants :	from 0.5 % to 10 % by weight

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More interesting core compositions are :

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cisapride-(L)-tartrate :	from 8 to 12 % by weight
filler :	from 55 to 65 % by weight
hydrophilic polymer mixture :	from 20 to 25 % by weight
lubricants :	from 2.5 % to 8 % by weight

5

Particular core compositions are :

cisapride-(L)-tartrate :	about 9 % by weight
filler :	about 61 % by weight
10 hydrophilic polymer mixture :	about 23.5 % by weight
lubricants :	about 6.5 % by weight

Preferred core compositions are :

15 cisapride-(L)-tartrate :	about 9 % by weight
lactose :	about 61 % by weight
hydroxypropyl methylcellulose:	from 5.5 % to 18 % (*)
hydroxypropyl cellulose	from 5.5 % to 18 % (*)
lubricants :	about 6.5 % by weight

20

(*) the total amount of cellulose derivatives in weight percent being about 23.5 %

In view of the gastro-intestinal motility stimulating properties of cisapride, the present invention provides the use of the present formulation as a medicine, in particular in

25 treating gastro-intestinal disorders.

Experimental partExample 1

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To a stirred solution of cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide (4 g) in ethanol (81 ml) was added a solution of [R(R*,R*)]-2,3-dihydroxybutanedioic acid (1.4 g) in ethanol (20 ml) and the product was allowed to crystallize. It was filtered off and dried, yielding 4.8 g (89%) of

35 (+)-cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide [R(R*,R*)]-2,3-dihydroxybutanedioate (1:1), i.e. cisapride-(L)-tartrate. Melting point is 197.1 °C and $[\alpha]_D^{20}$ is 6.7 (c = 0.1 % methanol).

Example 2

Ingredients for the preparation of 1000 tablets (570 mg) of formulation 1 :

5	Ingredient	amount	% of tablet weight
	cisapride-(L)-tartrate	52.92 g	9.3 %
	Lactose	346.08 g	60.7 %
10	Hydroxypropylmethylcellulose 2208	66 g	11.6 %
	Klucel EF ®	67.95 g	11.9 %
	water (*)	60 g	
	isopropanol (*)	140 g	
	magnesium stearate	2.85 g	0.5 %
15	Aerosil ®	5.7 g	1.0 %
	talc	28.5 g	5.0 %

(*) these ingredients are not comprised in the final composition of the tablet.

20

Preparation :

The above mentioned amounts of cisapride-(L)-tartrate, lactose, hydroxypropylmethyl-cellulose, Klucel EF® were sieved over a stainless-steel frame sieve (mesh 0.95 mm) and were mixed in a planetary powder mixer during 5 minutes. The mixture was wetted with isopropanol and water. The wetted mixture was again sieved over a frame sieve (mesh : 1.8 mm). The mixture was dried overnight at a temperature of 45 °C. The dried granulate was sieved over a frame sieve (mesh : 0.95 mm). The dried and sieved granulate was mixed with sieved magnesium stearate, Aerosil ® and talc in a planetary powder mixer during 5 minutes.

30

Preparation of tablets :

Using the above described mixture 1000 tablets were compressed.

35

Example 3

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Ingredients for the preparation of 1000 tablets (tablets of 570 mg) of formulation 2 :

	Ingredient	amount	% of tablet weight
5			
	cisapride-(L)-tartrate	52.92 g	9.3 %
	lactose	346.08 g	60.7 %
	Hypromellose 2208	40 g	7.0 %
	Klucel EF ®	93.95 g	16.5 %
10	water (*)	45 g	
	isopropanol (*)	105 g	
	magnesium stearate	2.85 g	0.5 %
	Aerosil ®	5.7 g	1.0 %
	talc	28.5 g	5.0 %

15

(*) these ingredients are not comprised in the final composition of the tablet.

Preparation is completely analogous to the preparation as described for formulation 1.

20 Example 4

Ingredients for the preparation of 1000 tablets of formulation

	cisapride-(L)-tartrate	52.92 mg
25	lactose monohydrate	346.08 mg
	Hypromellose 2208 15000mPa.s	66 mg
	Hydroxypropylcellulose	67.95 mg
	water (*)	
	isopropanol (*)	
30	magnesium stearate	2.85 mg
	Aerosil®	5.7 mg
	Talc	28.5 mg

Coating composition

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	Hypromellose 2910 5mPa.s	12 mg
	propylene glycol	3 mg

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titanium dioxide	3 mg
talc	2 mg
water (*)	120 mg

5 Preparation

Cisapride-(L)-tartrate, lactose, Hypromellose and Klucel® are mixed in a high shear mixture-granulator and wetted with a mixture of isopropanol and water. The granulate thus formed is dried by heating in vacuo. After calibrating the dried granulate aerosil, talc and magnesium stearate are added and mixed till a homogeneous mixture is obtained. Biconvex tablets with a diameter of 11.5 mm weighing about 570 mg are compressed.

The tablets are coated in a suitable coating vessel with a coating suspension consisting of hypromellose (5 mPa.s), propyleneglycol, titanium dioxide, talc and water.

15

Claims

1. An extended release formulation comprising cisapride-(L)-tartrate suitable for oral administration.
- 5 2. An extended release formulation as claimed in claim 1 comprising a mixture of hydroxypropyl methylcellulose and another viscous cellulose polymer.
- 10 3. An extended release formulation as claimed in claim 2 comprising a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose.
- 15 4. An extended release formulation as claimed in claim 2 wherein the core of the formulation comprises from 15 % to 35 % of the mixture of hydroxypropyl methylcellulose and another viscous cellulose polymer.
- 20 5. An extended release formulation as claimed in claim 4 wherein the ratio of the weight of hydroxypropyl methylcellulose over the weight of hydroxypropylcellulose ranges from about 0.33 to about 3.
- 25 6. An extended release formulation as claimed in claim 5 wherein the ratio of the weight of hydroxypropyl methylcellulose over the weight of hydroxypropylcellulose is about 1.
- 25 7. An extended release formulation as claimed in any of claims 1 to 4 comprising :

cisapride-(L)-tartrate :	about 9 % by weight
lactose :	about 61 % by weight
hydroxypropyl methylcellulose:	from 5.5 % to 18 %
hydroxypropyl cellulose	from 5.5 % to 18 %
lubricants :	about 6.5 % by weight,
- 30 the total weight percent of cellulose derivatives being about 23.5 %.
8. A crystalline form of cisapride-(L)-tartrate wherein the diastereomers [(3R4S)(2R3R)] and [(3S4R)(2R3R)] crystallize as a double salt in a 1:1 ratio.
- 35 9. Process of preparing an extended release formulation as claimed in any of the claims 1 to 7 characterized in that the active ingredient is intimately mixed with the other pharmaceutically acceptable ingredients.
- 40 10. Use of a composition as claimed in any of claims 1 to 7 for use as a medicine, especially for treating gastro-intestinal disorders.